UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MILTON DAVID GOLDENBERG

Appeal No. 2006-0656
Application No. 10/086,637

ON BRIEF

Before SCHEINER, MILLS and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This present invention is directed to a method for close-range immunological detection and visualization of tumors and other lesions. The examiner has rejected the claims under 35 U.S.C. § 103, and under the doctrine of obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 134. We affirm the double patenting rejection, but reverse the obviousness rejection.

Background

The present invention is directed to short-range immunological detection of a tumor or other lesion "in the course of [an] intraoperative, laparoscopic, intravascular, [or] endoscopic" procedure (Specification, page 1). The primary detection reagent is a

bispecific antibody fragment with a molecular weight of 85,000 daltons or less (such as a divalent single chain $(sFv)_2$ or $(sFv')_2$ fragment), which has a first binding site specific for an antigen associated with the lesion, and a second binding site specific for a bivalent labeled hapten. Id., page 26.

According to appellant, a bispecific antibody fragment with a molecular weight of 85,000 daltons or less is "critical" (Appeal Brief, page 10) to the claimed invention because an antibody fragment of this size is small enough to be "cleared quickly and naturally through the kidneys . . . so that targeting [and detection] can be effected within 48 hours" (Specification, pages 4-5) with minimal background interference (id., page 2). Fab and Fab' fragments (about 50,000 and 55,000 daltons, respectively) are small enough to be cleared rapidly, but are unsuitable for the claimed method because they are monovalent, and cannot bind both antigen and labeled hapten (id., page 26). On the other hand, $F(ab)_2$ or $F(ab')_2$ fragments (about 110,000 daltons for IgG), although divalent, are "too large to be filtered through the glomerular basal membrane[,] . . . must be catabolized elsewhere" first, and take much longer to clear, "unduly delay[ing] other procedures" (id.).

The Claims

Claims 183-193, 196 and 197 are pending and the subject of appeal. Claims 99-182, 194, 195 and 198-201 are also pending, but have been withdrawn from consideration. Claim 183 is representative of the subject matter on appeal:

183. A method of close-range detection of lesions during an operative, endoscopic, laparoscopic, intravascular catheter, or surgical procedure, wherein the method comprises:

(a) injecting a patient who is to undergo such a procedure with a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less, wherein the bispecific antibody fragment has a first antibody binding site which specifically binds to an antigen produced or associated with a lesion, and has a second antibody binding site which specifically binds to a hapten, and permitting the antibody fragment to accrete at target sites;

(b) injecting a bivalent labeled hapten, which quickly localizes at the target site and clears through the kidneys; and

(c) detecting the presence of the hapten by close-range detection of elevated levels of accreted label at the target sites with detection means, within 48 hours of the first injection, and conducting said procedure.

Discussion

Obviousness

The examiner rejected claims 183, 187-189, 191-193, 196 and 197 under 35 U.S.C. §103 as unpatentable over Goldenberg[1] in view of Barbet.[2] In addition, the examiner rejected claim 190 under 35 U.S.C. §103 as unpatentable over Goldenberg and Barbet, and further in view of Horowitz.[3] We consider the examiner's proposed combination of Goldenberg and Barbet to be central to both rejections, so we will discuss the rejections together.

Goldenberg describes "short-range intraoperative or endoscopic tumor detection," wherein a patient is injected with a radiolabeled primary antibody which specifically binds a tumor marker, and a surgically exposed or endoscopically accessed body cavity is scanned at close range to detect accretion of the labeled antibody

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[1] Goldenberg, U.S. Patent 4,932,412, issued June 12, 1990
[2] Barbet et al., U.S. Patent 5,256,395, issued October 26, 1993
[3] Horowitz, U.S. Patent 4,706,652, issued November 17, 1987

(Goldenberg, column 2, lines 6-16). "[D]iscrimination between tumor and non-tumor tissue is enhanced" (id., column 1, lines 63-64) by injecting a "contrast or subtraction agent radiolabeled with a radioisotope emitting at an energy which is separately detectable from the primary antibody label" (id., column 2, lines 19-21) and an "unlabeled second antibody which specifically binds the primary antibody or the labeling moiety thereof . . . in an amount sufficient to reduce the circulating level of the primary antibody label by at least about 10-85%" (id., lines 49-56). Finally, Goldenberg teaches that "[t]he antibody used as the primary imaging agent . . . may be whole IgG, IgA, IgD, IgE, IgM and the like, or a fragment such as, e.g., $F(ab')_2$, $F(ab)_2$, Fab', Fab or the like" (id., column 6, lines 50-54).

Barbet describes an immunodiagnostic method comprising "intravenous injection of a suitable dose of [a] dual specificity conjugate, together with, or followed . . . by, injection of [a] radioactive affinity enhancement probe . . . to allow detection of [ ] target cells by [an] imaging device" (Barbet, column 8, lines 51-57). The dual specificity conjugate is trivalent (at least), with two or more binding sites specific for antigen(s) expressed on the surface of the target cells, plus at least one hapten specific binding site (id., column 5, lines 1-12). The dual specificity conjugate preferably comprises "$F(ab')_2$ fragments of about 100,000 Da, or Fab or Fab' fragments of about 50,000 Da" (id., column 6, lines 32-35), and may be, for example, "an $F(ab')_2$ recognizing a cell membrane target antigen, coupled to an Fab' recognizing [a] hapten" (id., column 5, lines 9-11). "[T]he affinity enhancement probe comprises at least two hapten groups and one or several effector groups" (id., column 4, lines 49-50). According to Barbet, the affinity enhancement probe has a "definite tropism towards cell-bound, as opposed

to excess free, dual specificity conjugate" inasmuch as "multiple simultaneous binding to receptors distributed at the external side of the . . . target cells may be much stronger than monovalent binding to the same receptors in solution" (id., column 4, lines 22-31).

According to the examiner, "[i]t would have been obvious to one of ordinary skill in the art to modify the methods of radiodiagnosis disclosed by Goldenberg by administering a radiolabeled hapten and a bispecific antibody having a second binding site to the hapten" because Barbet teaches that "methods of radiodiagnosis . . . can be made more effective by [ ] a two-step approach of administering a bispecific antibody and a labeled hapten, wherein the bispecific antibody has a binding site for both the target . . . and the hapten" (Examiner's Answer, page 4).

Even if we were to accept the examiner's reasoning regarding a "two-step" versus "one-step" approach, however, we note that, at a minimum, the examiner has not adequately addressed the claims' requirement for "a bispecific antibody fragment or subfragment with a molecular weight of 85,000 daltons or less" (e.g., claim 183).

It is fair to say that both Goldenberg and Barbet teach "that antibody fragments (such as[ ] Fab and Fab' fragments . . .) are [ ] useful and/or art recognized equivalents to other antibodies" and their use "is commonplace in radioimmunodiagnostics" (Examiner's Answer, page 8). It is also the case that Fab and Fab' fragments have molecular weights of less than 85,000 daltons. However, Fab and Fab' fragments are monovalent, and therefore, cannot possibly meet the present claims' requirement for a "bispecific antibody fragment" with "a first antibody binding site which specifically binds to an antigen . . . and [ ] a second antibody binding site which specifically binds to a hapten" (e.g., Claim 183).

Nor do we find anything in Goldenberg or Barbet which would have led one skilled in the art to use a divalent fragment with a molecular weight of 85,000 daltons or less. As appellant points out, Goldenberg "is concerned with . . . a method of reducing background radiation so as to obtain an accurate reading of the radiation associated with the primary antibody that binds the tumor antigen" (Appeal Brief, page 8), and "it doesn't really matter what type of antibody is used as the primary antibody" (id., page 9). Barbet, on the other hand, does suggest that dual specificity conjugates comprising various combinations of antibody fragments are preferable to conjugates comprising whole antibodies, but all of Barbet's dual specificity conjugates are trivalent (at least), with two or more binding sites for antigen, and one or more for hapten, and are considerably larger than the divalent fragments required by the present claims (Barbet, columns 4 and 5, and Example 1). Moreover, "clearance of [ ] excess dual specificity conjugate" is not an issue in Barbet's method because clearance "is not required prior [to] injection of the [affinity enhancement probe]" (id., column 9, lines 4-6).

Much has been said on both sides about the propriety of combining Goldenberg and Barbet, but the bottom line is, quite simply, neither reference describes or suggests the use of an antibody fragment that has two binding sites and a molecular weight of 85,000 daltons or less. Horowitz, cited with respect to claim 190 as evidence that brachytherapy via endoscope or catheter is conventional, does nothing to remedy this deficiency.

"[T]he examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28

USPQ2d 1955, 1956 (Fed. Cir. 1993). On this record, we find that the examiner's initial burden of providing the evidence necessary to establish a prima facie case of unpatentability has not been met. Accordingly, the rejections of the claims under 35 U.S.C. § 103 are reversed.

Obviousness-Type Double Patenting

The examiner rejected claims 183-193, 196 and 197 under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,387,350. Appellant does not dispute the merits of the examiner's double patenting rejection, and indicates that a terminal disclaimer will be filed "upon remand to the examiner with the reversal of the outstanding prior art rejections" (Appeal Brief, page 14). Thus, we affirm the rejection.

Summary

We affirm the examiner's rejection of claims 183-193, 196 and 197 under the doctrine of obviousness-type double patenting, but reverse the rejections of claims 183, 187-193, 196 and 197 as obvious over the prior art.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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Administrative Patent Judge)
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